OPHTHALMIC TREATMENT BY TOPICAL ADMINISTRATION OF CYCLOSPORIN

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to cyclosporin treatment of traumatic or surgical phacoanaphylaxis endophthalmitis, or uveitis.

2. Description of the Prior Art

Phacoanaphylactic endophthalmitis and uveitis are diseases of the eye which can be located throughout the eye; in both the posterior and anterior chambers of the eye as well as the vitreous body.

Uveitis, the inflammation of the uvea, is responsible for about 10% of the visual impairment in the United States. Phacoanaphylactic endophthalmitis is a human autoimmune disease.

Panuveitis refers to inflammation of the entire uveal (vascular) layer of the eve. Posterior uveitis generally refers to chorioretinitis and anterior uveitis refers to iridocyclitis. The inflammatory products (i.e., cells, fibrin, excess proteins) of these inflammations are commonly found in the fluid spaces of the eye, i.e., anterior chamber, posterior chamber and vitreous space as well as infiltrating the tissue imminently involved in the inflammatory response. Uveitis may occur following surgical or traumatic injury to the eye; as a component of an autoimmune disorder, i.e., rheumatoid arthritis, Behcet's disease, ankylosing spondylitis, sarcoidosis; as an isolated immune mediated ocular disorder, i.e., pars planitis, iridocyclitis etc., unassociated with known etiologies; and following certain systemic diseases which cause antibody-antigen complexes to be deposited in the uveal tissues. Together these disorders represent the non-infectious uveitities.

The normal eye is protected from immune surveillance by blood barriers which do not allow free migration of cells or proteins into the eye. When the eye is injured or when vasculitis occurs, the internal ocular structures are exposed to the general immune system and frequently elicit autoimmune responses.

Phacoanaphylaxis is a severe form of uveitis in which the lens is the causitive antigen. The lens proteins are normally secluded by the lens capsule since before birth. When these proteins are released into the eye by injury or surgery or occasionally during cataract development, they can become intensely antigenic and incite an autoimmune response. If the response is moderate it is seen as a chronic uveitis. If it is very fast in progression they eye becomes severely inflamed in all segments. This latter response is named phacoanaphylaxis.

Cyclosporins are unique immunosuppressive agents derived from an extract of soil fungi. Cyclosporine A was first proposed for use as an antifungal agent but its immunosuppressive effects were found to be more marked than its antibiotic potential. This drug inhibits the generation of effector T-lymphocytes without inhibiting the expression of suppressor lymphocytes.

Cyclosporin's immunosuppressive properties has led to its use in immune system related diseases. In ophthalmic applications, cyclosporin has been used topically for the treatment of eye surface (e.g., cornea) related diseases.

For example, Hunter et al (*Clin. Exp. Immunol.* (1981), 45, pp. 173–177) has administered cyclosporin topically in a rabbit model of corneal graft rejection with positive results. These effects were found to be attributable to T-cell suppression within the eye or within systemic compartments such as blood or lymph.

Boisjoly et al (Arch. Ophthalmol. (1984) 102:1804–1807) have reported that topical application of Cyclosporine had a beneficial prophylactic effect towards the treatment of severe herpetic stromal keratitis.

Mosteller et al (*Investigative Ophthalmol.* (1984) Supp. 23, 3, p. 38) propose the potential suppression of deleterious ocular immune reactions such as the eye surface cornea allograft reaction by applying a single dose of a 10% Cyclosporine A ointment in the lower culde-sac of rabbit eyelids.

In other ophthalmic applications, where the disease being treated is not limited to the eye surface, cyclosporin has been used systemically.

For example, Nussenblatt et al (*Amer. J. Ophthamol.* (1983), 96, pp. 275–282) has reported clinical improvement in some patients with noninfectious posterior uveitis following systemic treatment with Cyclosporin.

To date, uveitis has been treated by systemic administration of cyclosporin since this disease is not limited to the eye surface. However, systemic therapy with cyclosporin has serious drawbacks. First there is a high risk of adverse responses when cyclosporin is used systemically. For example, cyclosporin increases the severity of epithelial disease when antiviral coverage is not provided. Cyclosporine used systemically has also been associated with a high incidence of renal toxicity, some cases of hepatotoxicity, increased incidence of lymphoid tumors and increased incidence of opportunistic infections. It is only slightly less toxic than other immunosuppressive agents i.e., cyctoxan, aziothioprine which in addition to causing increased incidence of infections, are more irreversible in their effects than is cyclosporine. The systemic side effects of cyclosporine are so severe and so common that they preclude its use to life-threatening or in some cases severe sight-threatening disease. Finally, systemic application of cyclosporin is limited by its prohibitive cost.

Prior art understanding of the activity of cyclosporin towards ophthalmic traumatic uveitis has however rested on the theory that total body immunosuppression was necessary for efficacy. By requiring systemic administration in cyclosporin treatment of opthalmic diseases not limited to the eye surface, a patient has heretofore been required to assume a high risk of adverse immunological responses, this risk naturally being accompanied by high treatment expense due to the quantities of cyclosporin required in systemic therapy.

Accordingly there exists a strong need for the elimination of the undesirable physiological and economic problems associated with cyclosporin treatment of phacoanaphylactic endophthalamitis and uveitis, while maintaining the advantageous therapeutic properties of this treatment.

Applicants have now surprisingly discovered that although current ocular pharmacology dictates that topical medications in general are not useful for the treatment of opthalmic diseases found in the posterior or vitreous segments of the eye (see, e.g., Maurice et al, *Ocular Pharmacokinetics, in Pharmacology of Eye,* Sears, M. L., editor, Springer-Verlag publisher, New York (1984), pp. 19–102), the topical administration of a cyclosporin to the eye is efficatious in the treatment of phacoanaphylactic endophthalmitis or uveitis found